IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.:	10/621,803	Confirmation No: 5941
Applicant:	Browne	
Filed:	July 17, 2003	
For:	DEVICE FOR AMPLIFYING AND DETECTING A TARGET NUCLEIC ACID	
Examiner:	Teresa E. Strzelecka	
Group Art Unit:	1637	
Customer No.	21365	

SUBMISSION UNDER 37 C.F.R. § 1.114

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the communication mailed from the Patent and Trademark Office on July 24, 2006, please consider the following.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

AMENDMENTS TO THE CLAIMS

The following listing of claims will replace all prior versions and listings of claims in the Application.

Listing of Claims

44. (New) A device for amplifying and detecting a target nucleic acid, comprising:

a solid support bead having a surface;

an amplification primer immobilized to the surface of said solid support bead, said amplification primer comprising a promoter sequence for an RNA polymerase and a sequence complementary to a first strand of said target nucleic acid; and

a labeled hybridization probe immobilized to said surface,

wherein said labeled hybridization probe comprises a sequence complementary to an amplicon synthesized using said amplification primer and said target nucleic acid as a template in a nucleic acid amplification reaction, and

wherein prior to contact of said device with any nucleotide polymerizing enzyme said labeled hybridization probe comprises a detectable label and is immobilized to said surface.

45. (New) The device of Claim 44, wherein said surface comprises a material selected from the group consisting of glass and plastic.

46. (New) The device of Claim 45, wherein said amplification primer immobilized to said surface is covalently immobilized to the surface of said solid support bead.

47. (New) The device of Claim 45, wherein said labeled hybridization probe immobilized to said surface is covalently immobilized to the surface of said solid support bead.

48. (New) The device of Claim 45, wherein said amplification primer and said labeled hybridization probe are each covalently immobilized to the surface of said solid support bead.

49. (New) The device of Claim 44, wherein said labeled hybridization probe comprises a fluorephore moiety and a quencher moiety.

50. (New) The device of Claim 44, wherein said device comprises two labeled hybridization probes immobilized to said surface, and wherein said two labeled hybridization probes comprise different sequences.

51. (New) The device of Claim 50, wherein prior to contact of said device with any nucleotide polymerizing enzyme there is immobilized to the surface of said solid support bead only one amplification primer sequence having a 3'-end that can be extended by a DNA polymerase using as a template said first strand of the target nucleic acid or the complement thereof.

52. (New) The device of Claim 44, wherein prior to contact of said device with any nucleotide polymerizing enzyme there is immobilized to the surface of said solid support bead only one amplification primer sequence having a 3'-end that can be extended by a DNA polymerase using as a template said first strand of the target nucleic acid or the complement thereof.

53. (New) A kit for detecting a target nucleic acid, comprising:

a device in accordance with Claim 44;

a soluble oligonucleotide primer that is not immobilized to the surface of said solid support bead; and

a positive-control nucleic acid amplifiable in a nucleic acid amplification reaction using said amplification primer in combination with said soluble oligonucleotide primer.

REMARKS

Applicant acknowledges receipt of the Office Action mailed July 24, 2006.

The previously pending claims have been canceled and replaced by a corresponding set of new claims. New Claim 44 substantially corresponds to canceled Claim 1, but further includes the "promoter sequence" limitation set forth in canceled Claim 9, and specifies that the recited hybridization probe is immobilized prior to contact with any nucleotide polymerizing enzyme. Unlike canceled Claim 1, New Claim 44 does not recite "at least one species of..." which caused confusion over the number of oligos embraced by some dependent claims, and confusion over the biological origin of oligonucleotide sequences. New Claims 45-46 substantially parallel canceled Claims 2-3. New Claims 47-48 substantially parallel canceled Claims 4-5, but do not recite "each of said at least one species." Canceled Claim 6 finds no counterpart in the new claim set. New Claim 49 corresponds to canceled Claim 7. New Claim 50 recasts canceled Claim 32 by positively reciting a second labeled hybridization probe. New Claims 51-52 are patterned after canceled Claims 35 and 38, but do not recite the confusing term, "species," and more precisely address the upper limit number of immobilized primers. New Claim 53 parallels canceled Claim 19, but clarifies the recited "soluble" primer is one "that is not immobilized to said surface of said solid support bead." Canceled Claims 39-43, drawn to reaction mixtures, find no counterparts in the new claim set.

Claims 44-53 will be pending upon entry of this Amendment.

No new matter is being added by the amendments made herein.

Entry of this Response is respectfully requested.

The Rejection Under § 112, Second Paragraph

Claim 32

Claims 32 has been rejected under § 112, second paragraph, as being indefinite over the recitation of "wherein said at least one species of labeled hybridization probe comprises no more than two species of labeled hybridization probe." The Examiner pointed out an inconsistency in the claim language since "at least one" implies more than one, but "no more than two" means two, one or no probes.

New Claim 50, patterned after rejected and canceled Claim 32, does not recite the language which served as the basis of the rejection. Instead, New Claim 50 positively sets forth a device having two different labeled hybridization probes immobilized thereto. Accordingly, New Claim 50 is presented as complying with the requirements of § 112, second paragraph.

Claims 35 and 38

Claims 35 and 38 have been rejected under § 112, second paragraph, as being indefinite over the recitation of "wherein said at least one species of amplification primer comprises no more than a single species of amplification primer." The Examiner pointed out an inconsistency in the claim language since "at least one" implies more than one, but "no more than one" means one or no probes.

New Claims 51 and 52, patterned respectively after rejected and canceled Claims 35 and 38, do not recite the language which served as the basis of the rejection. Instead, New Claims 51 and 52 specify that, prior to contact with any nucleotide polymerase, the recited solid supports have immobilized thereto "only one" amplification primer having a 3'-end that can be extended

by a DNA polymerase. Applicant notes the Specification defines "amplification primer" on page 9 at lines 19-24. Accordingly, New Claims 51 and 52 are presented as complying with the requirements of § 112, second paragraph.

The Rejection Under § 102(b)

Claims 1-6, 19, 32, 35, 38 and 39 have been rejected under 35 U.S.C. § 102(b) as anticipated by the disclosure of U.S. Pat. No. 6,060,288, naming Adams et al., as inventors ("**Adams**" hereafter). The Action indicates that **Adams** instructs a device in accordance with Claim 1, where the recited "at least one species of labeled hybridization probe" is immobilized to the solid support bead by virtue of hybridizing to an amplicon that is attached directly to the bead. This immobilization is considered by the Examiner to represent covalent immobilization because the amplicon target of the probe is covalently immobilized, and so Claims 3-5 are said to be anticipated. The term "soluble" has been given no limiting weight (see Office Action, page 3 at §9) in Claim 19, and since **Adams** is said to instruct a positive control, that claim was said to be anticipated. The rejection of Claims 32, 35 and 38 appears based on interpretation of "species" of probes or primers as referring to an unspecified number of oligonucleotides specific for a "biological species." Finally, Claim 39 has been rejected because, in addition to disclosing the device of Claim 1, **Adams** teaches other relevant reaction mixture components. Applicant notes that the rejection of Claim 6 is no longer relevant because that claim has been canceled from the Application and finds no counterpart in the pending claim set.

The instant claims are presented as overcoming the § 102(b) rejection of the canceled claims. New Claim 44, patterned after canceled Claim 1, requires that, in addition to comprising a detectable label prior to contacting the claimed device with any nucleotide polymerizing enzyme, the labeled hybridization probe is immobilized to the surface of the solid support bead prior to contacting the claimed device with any nucleotide polymerizing enzyme. This limitation

is not found in the **Adams** reference. Support for the amendment can be found in the Specification, for example, in the paragraph bridging pages 13-14 describing composite arrays as comprising a solid support, at least one species of oligonucleotide primer, and at least one species of hybridization probe. The alternative use of a bead as the solid support is particularly recited on page 13 at lines 12-14. Additional support appears in working Example 9 which describes construction of a device comprising a composite array using chemically synthesized molecular beacon probes labeled with fluorescein. Only after the device included the immobilized hybridization probe was it contacted with reagents for performing a nucleic acid amplification reaction. Those reagents included a reverse transcriptase (*i.e.*, a DNA polymerizing enzyme) and a T7 RNA polymerase (*i.e.*, an RNA polymerizing enzyme). Notably, none of the newly presented claims recite "species," and so the aspect of the rejection based on the use of this term is no longer relevant. Finally, rejected kit Claim 19 has been recast as New Claim 53, and now specifies a soluble oligonucleotide primer "that is not immobilized to surface of said solid support." This limitation also is missing from **Adams**. Support for the claim language can be found in the Specification, for example, under Example 9 which describes construction and use of certain composite arrays. The Specification instructs on page 47 an immobilization chemistry used for covalently attaching molecular beacons to a solid support surface, and describes use of the resulting constructs by employing "soluble" primers, or use of the constructs after covalently coupling promoter primers comprising reactive amine groups, as described in Example 8 (see particularly page 47 at lines 20-23). In this instance the "soluble" primer is a primer not covalently attached to the solid support surface via a reactive amine, and this aspect of the invention is embraced in kit Claim 53.

The presently pending claims are submitted as novel over the prior art. Since the pending claims all require an amplification primer comprising a promoter sequence for an RNA polymerase, and since this limitation formerly was recited in canceled Claim 9 that was considered by the Examiner to be novel over **Adams**, New Claim 44 together with all claims

depending therefrom likewise must be considered novel. Accordingly, the instant claims are presented as being novel in light of the prior art.

The Rejections Under § 103(a)

I. The Rejection of Claim 7 Under § 103(a)

Claim 7, now canceled and substantially replaced by New Claim 49, has been rejected under 35 U.S.C. § 103(a) over the combined disclosure of **Adams** and Whitcombe et al., (*Nature Biotechn.*, **17**:804-807 (1999)) ("**Whitcombe**" hereafter). According to the rejection, **Adams** instructs fluorescently labeled probes, but fails to instruct the use of fluorophores and quenchers. **Whitcombe** instructs amplification of target nucleic acids using "Scorpion" primers which include both probe and primer elements. Since New Claim 44 includes the key limitations of canceled Claims 1 and 9, and in view of the relevance of the **Mueller** reference to canceled Claim 9 (*see* Section II, below), Applicant's comments concerning patentability of New Claim 49 are based on the combined disclosure of **Adams**, **Mueller** and **Whitcombe**.

There are at least three reasons why New Claim 49 must be considered nonobvious over the combined disclosure of **Adams**, **Mueller** and **Whitcombe**. First, New Claim 49, by virtue of its dependence on New Claim 44, requires an immobilized amplification primer that comprises a promoter sequence for an RNA polymerase. It would not have been obvious to have immobilized the Scorpion probe-primers of **Whitcombe**, either in combination with promoter-primers or modified to contain a promoter sequence for use in the transcription-based amplification reaction described by **Mueller**, because use of the resulting construct in the amplification reaction of **Mueller** would involve production of free amplicons, and so would substantially deviate from the principle of operation underlying the teaching of the primary prior art reference (*see* Section II, below). Second, activation of the probe component of the Scorpion

probe-primer requires a thermal denaturation step which is not a part of the isothermal 3SR reaction taught by **Mueller**. For example, **Whitcombe** under the first paragraph of the Results section describes real-time monitoring of amplification between cycles of PCR that involves denaturing and annealing to promote probe hybridization (*see* Fig. 1). In contrast, the 3SR isothermal amplification technique of **Mueller** does not employ thermal cycling, and so would not activate the Scorpion probe in a manner that would take advantage of the zero-order hybridization kinetics described by **Whitcombe**. Finally, use of the Scorpion probe-primers of **Whitcombe** immobilized in the device of **Adams** for use in transcription-based amplification techniques as taught by **Mueller** would seem contraindicated because such amplification techniques are known to synthesize substantial amounts of irrelevant amplification products. This fact is supported by the disclosure of **Mueller** in the paragraph bridging the columns on on page 434, which refers to "...evidence that a great deal of non-specific amplification takes place with 3SR, probably due to the fact that it takes place at such a relatively low temperature, allowing for non-specific annealing of primers." Indeed, **Mueller** actually observed the production of 3SR amplification products in target-negative controls – meaning that primers were consumed in the production of non-specific amplification products in the absence of nominal target. In view of the integral relationship between the probe and primer molecules that would be available on the surface of the suggested obvious device, and in view of the manner in which Scorpions are used, the ordinary skilled artisan would understand that amplification reactions generating nonsense primer extension products (*i.e.*, reactions using Scorpions in irrelevant primer extension reactions) would necessarily reduce the number of probe molecules available for hybridizing to authentic amplification products since the probe and primer components are parts of the same Scorpion molecule. Stated differently, extending a Scorpion primer in a transcription-based amplification reaction using an irrelevant template would effectively inactivate the probe component of that Scorpion molecule. Thus, employing the integral Scorpion probe-primer of **Whitcombe**, modified to include or be used in combination with a promoter sequence useful for conducting transcription-based amplification as taught by

Mueller, in the device of **Adams** would compromise the ability to detect target nucleic acids, particularly at low levels of input target.

Since the intended purpose of a device in accordance with the combined teaching of **Adams**, **Mueller** and **Whitcombe** would involve the production of free amplicons in a transcription based amplification reaction, since the primary reference instructs only the synthesis of amplification products that remain attached to the solid support, since isothermal transcription based amplification reaction of **Mueller** does not involve strand separation and annealing needed for activation of the probe component of a Scorpion probe-primer in accordance with **Whitcombe**, and since mistaken primer extension reactions characteristic of transcription based amplification reactions would inactivate Scorpion probes and reduce the utility of the suggested device, the invention of New Claim 49 cannot be considered *prima facie* obvious in light of the prior art of record.

II. The Rejection of Claims 9 and 40-42 Under § 103(a)

Claims 9 and 40-42 have been rejected under 35 U.S.C. § 103(a) over the combined disclosure of **Adams** and Mueller et al., (*Histochem. Cell Biol.* **108**:431-437 (1997)) ("**Mueller**" hereafter). The rejection indicates that **Adams** teaches amplification of RNA targets but fails to teach amplification using primers comprising a promoter for an RNA polymerase, and that **Mueller** teaches amplification of RNA targets using the "3SR" sequence replication method which uses a primer containing a T7 promoter sequence. According to the rejection, it would have been obvious for an ordinary skilled artisan to have used the 3SR reagents of **Mueller** in the device of **Adams** because **Mueller** instructs that the 3SR technique is simple to perform, there is no need for a thermal cycler or for heat stable enzymes, there is no need for denaturing conditions, etc. Applicant notes that Claims 40-42 have been canceled from the Application, and that Claim 9 has been canceled and substantially replaced by New Claim 44. Reasons why the

invention of New Claim 44 cannot be considered *prima facie* obvious over the cited combination of references are presented below.

It would not have been obvious for one of ordinary skill in the art to have created the suggested device of **Adams** in view of **Mueller** because doing so would have changed the principle of operation underlying the invention disclosed in the primary reference. **Adams**, in the Background section, particularly addresses the high rate of sample-to-sample contamination known to plague PCR procedures and presents solutions which universally involve synthesis of amplification products that remain attached to a solid support. Accordingly, the devices and methods disclosed by **Adams** involve retaining amplification products on a solid support, and avoiding production of amplicons that can diffuse or cause contamination. **Mueller** illustrates in Figure 1 the use of paired sets of primers in the 3SR isothermal amplification procedure, where each primer comprises a T7 promoter. As indicated by **Muller**, the purpose of the promoter is to serve as a recognition sequence for a T7 RNA polymerase, which transcribes sense and anti-sense RNA copies of a DNA positioned downstream of the promoter. Thus, substituting and using the 3SR reagents of **Mueller** in the device of **Adams** would have resulted in a system for creating RNA amplicons free in solution.

As articulated under M.P.E.P. § 2143.01, "[i]f the modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious." The principle of operation of the technique taught by **Adams** involves synthesizing amplification products that remain immobilized to a solid support. Immobilizing and using promoter-primers in accordance with the suggested obvious device of **Adams** in view of **Mueller** would result in production of free RNA amplicons, and so would go counter to the teaching of **Adams**. Because the principle of operation underlying the prior art invention being modified must be fundamentally changed to result in the suggested obvious device, the case for *prima*

facie obviousness of the instantly claimed invention should not be maintained. Accordingly, New Claim 44, which recites the limitation of canceled Claim 9, is presented as being nonobvious in light of the prior art.

III. The Rejection of Claim 43 under 35 U.S.C. § 103(a)

Claim 43 has been rejected under 35 U.S.C. § 103(a) over the combined disclosure of **Adams** and **Mueller**, further in view of Gerard et al., (*Mol. Biotech.* **8**:61-77 (1997)). Claim 43 has been canceled from the Application, and finds no counterpart among the instant claim set. Accordingly, the rejection of Claim 43 is no longer relevant.

CONCLUSION

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of all outstanding rejections are respectfully requested. Allowance of the claims at an early date is solicited. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the telephone number shown below.

Deposit Account Information

Please charge any fees due in connection with this submission, including the fees due under 37 C.F.R. § 1.17 for filing an RCE, to Deposit Account No. 07-0835 in the name of Gen-Probe Incorporated.

Respectfully submitted,

GEN-PROBE INCORPORATED

Dated: August 17, 2006

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